Post-diagnostic calcium channel blocker use and breast cancer mortality: a population-based cohort study

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Title: Post-diagnostic calcium channel blocker use and breast cancer mortality: a population-based cohort study

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Abstract

Background: There have long been concerns that calcium channel blockers (CCBs), widely used to treat hypertension, may contribute to malignant growth through the evasion of apoptosis and proliferation of cancer cells. Worryingly, a recent cohort study found breast cancer patients who used CCBs had higher death rates, however interpreting these results was difficult as they were based on all-cause mortality and medication use before cancer diagnosis. Therefore, we used UK population-based data to more robustly investigate the association between CCB use and cancer-specific mortality.

Patients and methods: We selected a cohort of patients with newly-diagnosed breast cancer between 1998 and 2012 from English cancer registries. We linked to prescription and clinical records from the Clinical Practice Research Datalink, and to death records from the Office for National Statistics. We used time-dependent Cox-regression models to calculate hazard ratios (HRs) comparing breast cancer-specific and all-cause mortality between post-diagnostic CCBs users and non-users, after adjusting for demographics, comorbidities and other medication use.

Results: Our cohort included 23,669 breast cancer patients, of which 5,141 used CCBs and 3,053 died due to their breast cancer during follow-up. After adjustment, CCB users had similar breast cancer-specific mortality to non-users (HR=0.98, 95% CI: 0.88, 1.08). There was no evidence of a dose-response relationship. We found similar associations for specific CCBs, and for all-cause mortality.

Conclusions: In this large population-based breast cancer cohort, we did not find any evidence that CCB use is associated with increased mortality. Our findings should reassure GPs that CCBs are safe to prescribe to breast cancer patients.

Keywords: breast cancer, calcium channel blockers, pharmacology, epidemiology

Key message: Although experimental evidence suggests that calcium channel blockers might contribute to malignant growth, our population-based study of 23,669 breast cancer patient did not find any association between medication use and breast cancer mortality. This could suggest that previous findings of increased deaths among users where partly driven by confounding by indication and other biases.

Introduction

Breast cancer is the second most common cancer in the world, with 1.7 million new cases diagnosed annually.[1, 2] Around 15% of patients die due to the disease within five years,[3] and they suffer markedly reduced quality of life, and substantially higher healthcare costs during treatment and recovery.[4-7]

Calcium channel blockers (CCBs) are a group of anti-hypertensive medications used to treat cardiovascular diseases such as hypertension and angina. In England, CCBs are recommended as the first-line treatment for hypertension, with around 40 million prescriptions dispensed annually.[8, 9] CCBs are also commonly used in the USA, with 6.5% of adults reporting using them within the last 30 days.[10] Despite their widespread use, there have long been concerns that CCBs may contribute to malignant growth through the evasion of apoptosis and proliferation of cancer cells.[11-13] In vitro and animal models have shown that CCBs reduce intracellular resting calcium concentration and inhibit apoptotic gene expression.[14, 15]

In humans, several studies have investigated the association between CCB use and breast cancer risk.[16] Although they have reached inconsistent conclusions, a recent meta-analysis concluded that long-term CCB use is associated with a statistically significant increase of 71% in breast cancer risk when compared to non-users.[16] The impact of CCB use on breast cancer progression has received much less attention. One study found a 22% increase in mortality among breast cancer patients who used CCBs when compared to non-users[17], however these findings are difficult to interpret because it did not identify cancer-specific deaths, adjust for comorbidities, test for a dose-response relationship, or assess CCB use after diagnosis. Consequently, we used population-based data from the UK to more robustly assess the association between CCB use and mortality among breast cancer patients.

Methods

Data Sources

Our study used data from the UK Clinical Practice Research Datalink (CPRD), linked to deprivation indices from census information, English cancer registry data from the National Cancer Data Repository (NCDR), and death registration data from the Office for National Statistics (ONS). The CPRD contains computerised medical records from 674 general practices (approximately 7% of the UK population) which are audited for data completeness and quality.[18] Practices meeting a predefined quality standard are deemed 'up to standard' and included in future extracts. Data recorded includes patient demographics, clinical diagnoses (using Read codes) and prescription medication use. Previous research has found CPRD prescription and clinical information to be of high quality.[18-20] The NCDR holds UK-wide data from English cancer registries compiled from a variety of sources including general practices, cancer screening programmes, NHS and private hospitals, and death certificates.[21] ONS death-registration data provide details on the date and cause(s) of death.

Study Design and Population

We used the NCDR to identify a cohort of female patients with newly-diagnosed breast cancer (ICD code C50) between 1998 and 2012. Cohort members with a previous record of cancer were identified and excluded from the analysis using a list of cancer Read codes modified for use in the CPRD.[22] Patients were excluded if they were diagnosed before they were registered with a CPRD practice, before their practice was deemed up to research standard, after they left a CPRD practice, or after data was last collected from their practice by the CPRD. A small number of patients were recorded within the NCDR more than once, when this occurred we used their first record. Patients with stage 0 breast cancer (ductal carcinoma in situ) were also excluded.

Deaths were identified from ONS records, and breast cancer specific deaths were defined as those with a primary cause of breast cancer (ICD code C50). Patients who died within the first year of the study were excluded as it is unlikely that these could be influenced by post-diagnostic medication use, therefore the follow-up period started from 1-year after diagnosis. The end of follow-up was the earliest date of death, end of registration with the practice, last collection of data from the practice, or last linkage between the CPRD and ONS death records.

Definition of exposure

We used the British National Formulary to compile a list proprietary and generic medication names for CCBs (Appendix 1). We added a lag of 12 months to CCB use as these medications are unlikely to have an immediate effect on breast cancer progression, and to prevent reverse causation.[23, 24] A diagram illustrating our design is shown in Appendix 2. We defined patients as users if they had at least one CCB prescription during the exposure period. Our medication data did not include details on whether the medication was dispensed, or eventually used by the patient. To enable the testing of dose-response relationships we extracted data on the medication prescribed, number of packs / tablets and medication strength, and calculated defined daily doses (DDDs). The DDD system is a validated measure of drug consumption maintained by the World Health Organisation.[25] A single DDD is the average maintenance dose per day of a drug used for its main indication in adults (e.g. hypertension for CCBs). There was insufficient information to calculate DDDs for 0.2% of prescriptions, and implausible values were recorded in a further 0.1% (e.g. 1 tablet; >50,000 tablets). In these cases we assumed the most common DDD based on other prescriptions with complete information. We calculated a running DDD total for each patient and identified the day when patients received their 1st (first use), 365th (one year's use), 1095th (three year's use) and 1825th (five year's use) DDD.

Covariates

Patients' age, smoking, alcohol, and obesity (BMI>30) data were determined from the closest GP record before breast cancer diagnosis (values more than 10 years before diagnoses were ignored). We used GP records to identify pre-diagnosis comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease), using a list of Read codes modified for use in the CPRD[22], as comorbidities have been consistently associated with higher cancer mortality.[26]

Deprivation data was available from census information, and based on the 2010 Index of Multiple Deprivation (IMD) score of the patient's postcode. The NCDR included detailed information about the patient's cancer, including diagnosis year, stage, histologic grade, and treatment (surgery, chemotherapy, and radiotherapy). We used CPRD prescription records to identify patients who received hormone therapy treatment (tamoxifen or aromatase inhibitors), and those who had used oral contraceptives or hormone replacement therapy (HRT) prior to diagnosis, as these have been shown to influence breast cancer progression previously.[27, 28]

Statistical analysis

We calculated descriptive statistics and compared the demographic and clinical characteristics of the CCB users and non-users, and calculated 1-, 2- and 5-year cancer specific survival probabilities. We used time-dependent Cox regression models to calculate hazard ratios (HRs) comparing breast cancer-specific death between CCB users and non-users. In our primary analysis we included CCB use as a time-varying covariate to avoid immortal time bias.[29] Therefore patients were initially included within the analysis as non-users until 12 months after their first use (due to the exposure lag), after which they were included as users. Our primary analysis adjusted for age at diagnosis, year of diagnosis, deprivation quintile, comorbidities (separate terms for each), prior use of HRT or oral

contraceptives, and treatment within six months of diagnosis (separate terms for surgery, chemotherapy, radiotherapy, tamoxifen, aromatase inhibitors). Comorbidities were not included as time-varying covariates due to the possibility that changes in health status could lie on the causal pathway between CCB use and breast cancer mortality. We repeated our analysis by number of DDDs prescribed (e.g. patients were included in the 1-364 DDD group until 12th months after they received their 365th DDD), and for each commonly prescribed CCB medication (≥2% usage in cohort).

Sensitivity and subgroup analyses

We conducted sensitivity analysis for all-cause mortality, and for cause-specific mortality where the definition of breast cancer death was expanded to include secondary causes of death. We also conducted sensitivity analysis with a lag period of zero (patients followed-up from diagnosis), six months (patients followed-up from six months after diagnosis) and two years (patients followed-up from two years after diagnosis). We performed two simplified analyses which controlled for immortal time bias without requiring time-varying covariates.[29] Firstly, we based CCB usage on the year after diagnosis, and restricted our analysis to patients living at least one year. Secondly, we based CCB usage on the year prior to diagnosis, and followed-up patients from the date of diagnosis. Diagrams illustrating the design of our sensitivity analyses which vary the exposure lag and/or period are given in Appendix 2. To facilitate comparison between studies we repeated our analysis using methods broadly similar to the previous *Holmes et al* analysis for all-cause, breast cancer and cardiovascular (ICD 10 codes: I0-I99, G45, Q20-26, F01) deaths. Specifically, we based CCB usage on the year prior to breast cancer diagnosis, did not adjust for comorbidities, and restricted the non-user group to those who did not receive any anti-hypertensive medication (diuretics, vasodilator antihypertensive drugs, centrally acting antihypertensive drugs, alpha-adrenoceptor blocking drugs, beta-blockers, ACEIs, ARBs, renin inhibitors, and calcium channel blockers) during the exposure period.

To ensure that confounding by indication was not driving our results we conducted three further sensitivity analysis restricted to patients with similar diagnoses. First, we restricted our analysis to patients with a record of hypertension (Read code categories G20 and 662) in the year prior to diagnosis. Second, we restricted our analysis to patients who used an anti-hypertensive medication in the year prior to breast cancer diagnosis. Third, we compared patients who received CCBs to those who received a different anti-hypertensive medication after diagnosis (using a time-varying covariate) as the use of an active comparison can overcome several common pharmacoepidemiological biases.[30]

We performed additional sensitivity analysis adjusting for cancer diagnosis details (stage, grade) and patient lifestyle (smoking, alcohol consumption, obesity) using complete-case and multiple imputation with chained equations (MICE). The MICE imputation used ordered logit models with age, deprivation, death indicator and the baseline hazard function as covariates.[31] Briefly, MICE is a simulation-based approach for handling missing data which leads to valid statistical inferences under certain circumstances.[32] Finally, we conducted a complete case analysis adjusting for cancer diagnosis details (stage, grade), but limited to patients registered with the Northern & Yorkshire Cancer Registry, the registry with the most complete staging information in England (92% of all patients). Restricting our analysis to patients with more complete data could help reduce potential biases due to missing confounder data. Lastly, we used the Fine and Gray sub-distribution hazard model to assess the impact of competing risks from non-breast cancer deaths.[33]

Results

Cohort Description

There were 54,190 breast cancer cases recorded within the NCDR between 1998 and 2012. We excluded 30,521 patients from the analysis, most commonly because they were diagnosed before they registered with a CPRD practice or before their practice was deemed up to research standard (n=12,418), they were diagnosed after they left a CPRD practice or data was last collected from it (n=9,989), they had a record of previous cancer (n=4,775), or they lived for less than 12 months after diagnosis (n=3,189). Therefore, our analysis cohort included 23,669 patients (126,154 person-years), of which 5,141 (21.7%) were CCB users (21,834 person-years). Median follow-up was 5.5 years (maximum 17.8 years). CCB users were more likely to be older, from a deprived area, have comorbidities, be treated with aromatase inhibitors, have lower stage cancer, be non- or ex-smokers, consume no alcohol, and be obese (Table 1).

Association between CCB use and mortality

Overall, CCB users were at a higher risk of breast cancer death than non-users (unadjusted HR=1.13, 95% CI: 1.03, 1.25; Table 2). Consequently, cancer-specific survival was slightly lower among CCB users at 1- (0.96 vs. 0.97), 2- (0.93 vs. 0.94) and 5-years (0.86 vs. 0.88) from start of follow-up. However, after adjustment for demographics, comorbidities, treatment and other medication use, CCB users had a similar risk of breast cancer death (adjusted HR=0.98, 95% CI: 0.88, 1.08). There was no evidence of a dose-response relationship; we observed small differences in breast cancer death even when comparing non-users to those who received at least 1,825 DDDs (adjusted HR=0.97, 95% CI=0.76, 1.24). Similarly, there was no evidence of an association between medication use and breast cancer death for any of the four specific CCBs included in our analysis, with adjusted HRs ranging from 0.95 (95% CI: 0.77, 1.19) for felodipine to 1.05 (95% CI: 0.93, 1.19) for amlodipine (Table 2).

Sensitivity and subgroup analyses

Our results were similar in the simpler analysis basing CCB use on the first year after diagnosis (Table 3). Classifying CCB using the year prior to diagnosis lead to a slightly higher association (adjusted HR=1.06, 95% CI: 0.95, 1.19), although this was broadly consistent with our main analysis. CCB users had a much higher risk of all-cause death (unadjusted HR: 1.59, 95% CI: 1.49, 1.69), however this was substantially attenuated to 1.04 (95% CI: 0.97, 1.11) after adjustment. Our results were robust to changes in the exposure lag period from zero to two years, when expanding our breast cancer-specific death definition to include secondary causes, when accounting for competing causes of death, and did not change appreciably when adjusting for cancer diagnosis (i.e. stage, grade) or patient lifestyle factors using complete case or multiple imputation methods. We observed broadly similar hazard ratios when restricting our analysis to patients with a prior diagnosis of hypertension (0.89; 95% CI: 0.71, 1.12), to those in receipt of anti-hypertensive medications before diagnosis (0.95; 95% CI: 0.84, 1.07), or when comparing CCB users to patients receiving a different anti-hypertensive medication after breast cancer diagnosis (1.02; 95% CI: 0.92, 1.13). When repeating the analysis using similar methods to *Holmes et al*, we found substantially higher all-cause mortality among CCB users (HR=1.27; 95% CI: 1.17, 1.38), but this largely reflected cardiovascular (HR=2.22; 95% CI: 1.81, 2.72) rather than breast cancer (HR=1.11; 95% CI: 0.98, 1.25) deaths.

Discussion

Summary of main findings

In this large, population-based cohort of newly-diagnosed breast cancer patients, we did not observe any evidence of an increase in breast cancer-specific mortality with CCB use after adjustment for patient demographics, comorbidities and other medication use. There was no evidence of a dose-response relationship. We found similar associations for specific CCBs and for all-cause mortality.

Strengths and weaknesses

Our study is the first to investigate post-diagnosis CCB use and breast cancer-specific mortality. It is based on a high-quality population-based cohort of patients with registry-confirmed breast cancer[18], and is more than five-times larger than previous work.[17] Patients included in the study had a long follow-up period after diagnosis of up to 17 years, which should allow any clinically important effect of CCBs on breast cancer progression to become apparent. Linkage to ONS death registration data allowed robust verification of death, and facilitated a breast cancer-specific analysis, which should be more sensitive to small-changes in disease-specific mortality, and less susceptible to confounding by indication than all-cause deaths.[24, 34] Although some misclassification of death cause is possible, studies have shown this is likely to have a limited impact on our estimates (as there is no obvious mechanism for differential misclassification)[35] and our results were similar when expanding our breast-cancer death definition to include secondary causes.

We used prescribing data collected as part of routine clinical care which accurately reflects GP prescribing practices and negates the risk of recall bias. This data also included detailed information on the type of CCB, and the strength, quantity and timing of prescription, which allowed us to investigate dose-response relationships, and conduct separate analysis for specific medications.

CCBs are not available over-the-counter in the UK, which negates exposure misclassification due to over-the-counter usage.

Our study has several potential weaknesses. It is observational and hence open to confounding. Although we have adjusted for several of the key determinants of breast cancer progression (e.g. age, comorbidities and treatment), some risk factors, including ethnicity and nutrition, were not available within our dataset.[36, 37] Other important prognostic variables such as cancer stage and grade were incomplete, and so omitted from our primary analysis. The reason stage was not available for a high proportion of breast cancer patients within the NCDR is unclear, however similar patterns have been reported elsewhere.[38] Nevertheless, the findings from our sensitivity analyses suggest that confounding or missing data issues were not solely driving our results. For example, our conclusions were unchanged when using multiple imputation to adjust for cancer stage and grade, or restricting our analysis to a single registry with almost complete staging data. Moreover, we observed little evidence of an association when using other antihypertensive medications as an active comparator (which should be confounded in a similar way to CCBs). The proportion of patients receiving surgery is slightly lower than reported in note reviews from Northern Ireland (which has a similar healthcare system to England)[41], suggesting that some misclassification of cancer treatment is possible.

Lastly, we do not know if patients adhered to their prescribed medications, however our main conclusions were similar when restricting our analysis to patients who received multiple prescriptions (>1,825 DDDs), where non-compliance is less of a concern.

Comparison with previous work

We are unaware of any other studies which have compared breast-cancer specific mortality between CCB users and non-users. One recent cohort study of 4,019 Canadian patients with registry-

confirmed breast cancer by *Holmes et al* reported a 22% (HR= 1.22; 95% CI: 1.02, 1.47) increase in all-cause mortality among CCB users.[17] However, this study did not examine post-diagnostic mediation use, did not investigate cancer-specific mortality, could not adjust for comorbidities, restricted their non-user group to patients not receiving anti-hypertensive medications, and had much shorter follow-up (maximum of 6 years) than our study. We found a comparable increase of 27% (HR= 1.27; 95% CI: 1.17, 1.38) in our cohort when using similar methods to those employed by *Holmes et al,* which was largely driven by cardiovascular deaths (HR= 2.22; 95% CI: 1.81, 2.72), suggesting that their estimates may have been substantially inflated by these potential weaknesses.

Implications for practice

CCBs are a widely used and effective treatment for cardiovascular conditions such as hypertension and angina. Although concerns have persisted that their use may lead to malignant growth through increased apoptotic evasion and cancer cell proliferation[11-13], our study suggests that this does not manifest in increased breast-cancer mortality. Consequently, general practitioners and patients with breast cancer should not be unduly concerned when prescribing or taking these medications.

Conclusions

In this large population-based cohort of patients with registry-confirmed breast-cancer, we did not find any evidence that CCB use is associated with increased mortality. Our findings should reassure GPs that they are safe to prescribe these medications to this patient group.

Disclosures

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Conflict of Interest: The authors have declared no conflicts of interest

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Tables and Figures

Table 1: Patient characteristics by CCB use at any time after diagnosis, restricted to patients living more than 1 year after diagnosis.

	All Patients	CCB Use	
		Non-user	User
Number of Patients	23,669	18,528	5,141
Person Years	126,154	104,320	21,834
Year of Diagnosis			
1998-2002	5,738 (24.2%)	4,316 (23.3%)	1,422 (27.7%)
2003-2007	8,776 (37.1%)	6,756 (36.5%)	2,020 (39.3%)
2008-2012	9,155 (38.7%)	7,456 (40.2%)	1,699 (33.0%)
Age at Diagnosis (SD)	61.9 (14.0)	59.9 (14.1)	68.8 (11.3)
0-49	4,774 (20.2%)	4,550 (24.6%)	224 (4.4%)
50-59	5,913 (25.0%)	5,041 (27.2%)	872 (17.0%)
60-69	5,955 (25.2%)	4,360 (23.5%)	1,595 (31.0%)
70-79	4,037 (17.1%)	2,577 (13.9%)	1,460 (28.4%)
80+	2,990 (12.6%)	2,000 (10.8%)	990 (19.3%)
Deprivation Quintile			
1 (Least Deprived)	6,026 (25.5%)	4,901 (26.5%)	1,125 (21.9%)
2	6,087 (25.7%)	4,717 (25.5%)	1,370 (26.7%)
3	4,873 (20.6%)	3,846 (20.8%)	1,027 (20.0%)
4	3,941 (16.7%)	3,013 (16.3%)	928 (18.1%)
5 (Most Deprived)	2,733 (11.6%)	2,043 (11.0%)	690 (13.4%)
Missing	9	8	1
Comorbidities			
Chronic Pulmonary Disease	2,716 (11.5%)	1,985 (10.7%)	731 (14.2%)
Diabetes	1,456 (6.2%)	839 (4.5%)	617 (12.0%)
Renal Disease	1,076 (4.5%)	646 (3.5%)	430 (8.4%)
Cerebrovascular Disease	650 (2.7%)	406 (2.2%)	244 (4.7%)
Congestive Heart Disease	345 (1.5%)	241 (1.3%)	104 (2.0%)
Peripheral Vascular Disease	264 (1.1%)	134 (0.7%)	130 (2.5%)
Myocardial Infarction	250 (1.1%)	160 (0.9%)	90 (1.8%)
Peptic Ulcer Disease	238 (1.0%)	162 (0.9%)	76 (1.5%)
Liver Disease	45 (0.2%)	33 (0.2%)	12 (0.2%)
Confounder Medications			
Hormone Replacement Therapy	7,002 (29.6%)	5,693 (30.7%)	1,309 (25.5%)
Oral Contraceptive	6,009 (25.4%)	5,132 (27.7%)	877 (17.1%)
Prior CCB Use	2,802 (11.8%)	309 (1.7%)	2,493 (48.5%)
Treatment			
Surgery	19,218 (81.2%)	15,040 (81.2%)	4,178 (81.3%)
Tamoxifen	14,445 (61.0%)	11,358 (61.3%)	3,087 (60.0%)
Aromatase inhibitors	11,914 (50.3%)	8,996 (48.6%)	2,918 (56.8%)
Radiotherapy	8,320 (35.2%)	6,298 (34.0%)	2,022 (39.3%)
Chemotherapy	6,774 (28.6%)	5,968 (32.2%)	806 (15.7%)
Grade			
1	3,780 (17.9%)	2,846 (17.3%)	934 (20.1%)
2	10,282 (48.7%)	7,926 (48.1%)	2,356 (50.8%)
3	7,039 (33.3%)	5,698 (34.6%)	1,341 (28.9%)
4	19 (0.1%)	14 (0.1%)	5 (0.1%)
Missing	2,549	2,044	505
Stage			
1	4,791 (49.0%)	3,748 (48.3%)	1,043 (51.5%)
2	3,936 (40.2%)	3,135 (40.4%)	801 (39.6%)
3	748 (7.6%)	611 (7.9%)	137 (6.8%)

4	309 (3.2%)	265 (3.4%)	44 (2.2%)
Missing	13,885	10,769	3,116
Smoking			
No	12,980 (61.3%)	10,126 (61.3%)	2,857 (61.3%)
Ex	4,675 (22.1%)	3,516 (21.3%)	1,153 (24.7%)
Yes	3,523 (16.6%)	2,876 (17.4%)	650 (13.9%)
Missing	2,491	2,010	481
Alcohol			
No	3,406 (19.7%)	2,449 (18.3%)	960 (24.3%)
Ex	350 (2.0%)	245 (1.8%)	103 (2.6%)
Yes	13,574 (78.3%)	10,678 (79.9%)	2,895 (73.1%)
Missing	6,339	5,156	1,183
Obesity			
Normal	7,724 (41.0%)	6,389 (44.0%)	1,333 (31.0%)
Overweight	6,324 (33.6%)	4,768 (32.8%)	1,559 (36.2%)
Obese	4,777 (25.4%)	3,366 (23.2%)	1,410 (32.8%)
Missing	4,844	4,005	839

Table 2: Association between CCB use and breast cancer mortality

	N	Person-Years	Deaths	Unadjusted HR	Age-adjusted HR	Fully-adjusted HR[a]
Calcium-channel blockers						
Never	18,528	104,320	2,522	Ref	Ref	Ref
Ever	5,141	21,834	531	1.13 (1.03,1.25)	0.93 (0.84,1.02)	0.98 (0.88,1.08)
1-364 DDDs	1,679	8,275	224	1.14 (0.99,1.31)	0.94 (0.82,1.08)	0.98 (0.85,1.13)
365-1094 DDDs	1,340	6,268	155	1.07 (0.91,1.26)	0.87 (0.73,1.02)	0.91 (0.77,1.08)
1095-1824 DDDs	841	3,237	82	1.31 (1.05,1.64)	1.07 (0.85,1.33)	1.13 (0.90,1.41)
1825+	1,281	4,054	70	1.10 (0.86,1.40)	0.90 (0.71,1.15)	0.97 (0.76,1.24)
Amlodipine						
Never	20,404	113,604	2,747	Ref	Ref	Ref
Ever	3,265	12,550	306	1.16 (1.03,1.30)	0.98 (0.87,1.10)	1.05 (0.93,1.19)
Felodipine						
Never	22,799	122,284	2,969	Ref	Ref	Ref
Ever	870	3,870	84	1.05 (0.84,1.30)	0.88 (0.71,1.10)	0.95 (0.77,1.19)
Nifedipine						
Never	23,035	122,954	2,966	Ref	Ref	Ref
Ever	634	3,200	87	1.24 (1.00,1.54)	1.04 (0.84,1.29)	0.97 (0.78,1.20)
Diltiazem						
Never	23,107	123,731	2,988	Ref	Ref	Ref
Ever	562	2,423	65	1.24 (0.97,1.59)	1.05 (0.82,1.34)	1.05 (0.82,1.34)

[a] Adjusted for age, deprivation, year of diagnosis, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery, tamoxifen, aromatase inhibitors), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (prior use of hormone replacement therapy, oral contraceptives).

Table 3: Sensitivity and subgroup analysis for CCB use and breast cancer mortality

	Non-Users[f]			Users			Unadjusted HR	Fully-adjusted HR[a]
	N	PY	Deaths[g]	N	PY	Deaths		
Main analysis	18,528	104,320	2,522	5,141	21,834	531	1.13 (1.03,1.25)	0.98 (0.88,1.08)
Death definition								
All-cause	18,528	104,320	4,032	5,141	21,834	1,259	1.59 (1.49,1.69)	1.04 (0.97,1.11)
Primary or secondary breast cancer cause	18,528	104,320	2,881	5,141	21,834	677	1.27 (1.16,1.38)	0.99 (0.91,1.09)
Exposure definition								
Year before diagnosis	20,875	134,349	2,661	2,794	15,474	392	1.25 (1.13,1.39)	1.06 (0.95,1.19)
Year after diagnosis	20,627	112,089	2,645	3,042	14,066	408	1.17 (1.05,1.30)	1.00 (0.89,1.11)
Exposure lag								
None	18,033	122,578	2,453	5,636	27,245	600	1.12 (1.02,1.22)	0.96 (0.88,1.06)
6 months	18,132	118,071	2,464	5,416	24,471	575	1.14 (1.04,1.25)	0.98 (0.89,1.08)
2 years	18,253	113,486	2,478	4,365	17,090	370	1.10 (0.98,1.23)	0.97 (0.86,1.09)
Hypertension diagnosis / treatment								
Pre-diagnosis hypertension diagnosis	1,396	7,487	199	1,287	5,806	137	0.99 (0.80,1.24)	0.89 (0.71,1.12)
Pre-diagnosis anti-hypertensive medication users	4,879	24,907	764	3,718	16,136	434	0.99 (0.88,1.12)	0.95 (0.84,1.07)
CCB vs. other anti-hypertensive medication	3,426	15,562	405	5,141	21,834	531	1.02 (0.90,1.16)	0.99 (0.87,1.12)
Holmes study methodology[b]								
All-cause deaths	15,080	100,242	2,710	2,794	15,474	883	2.14 (1.98,2.31)	1.27 (1.17,1.38)
Breast cancer deaths	15,080	100,242	1,856	2,794	15,474	392	1.34 (1.20,1.49)	1.11 (0.98,1.25)
Cardiovascular deaths	15,080	100,242	202	2,794	15,474	211	7.05 (5.80,8.56)	2.22 (1.81,2.72)
Adjustment								
CC lifestyle[c]	12,193	69,352	1,534	3,665	15,437	354	1.15 (1.03,1.29)	1.03 (0.91,1.17)
MI lifestyle	18,528	104,320	2,522	5,141	21,834	531	1.13 (1.03,1.25)	0.97 (0.88,1.07)
CC diagnosis[d]	7,327	40,504	808	1,924	7,895	169	1.18 (1.00,1.39)	1.06 (0.89,1.27)
CC diagnosis, most complete staging registry	1,312	7,102	178	330	1,420	34	1.06 (0.73,1.54)	1.03 (0.69,1.55)
MI diagnosis	18,528	104,320	2,522	5,141	21,834	531	1.13 (1.03,1.25)	0.97 (0.88,1.08)
Competing risks regression	18,528	104,320	2,522	5,141	21,834	531	1.10 (1.01,1.21)	1.05 (0.95,1.15)

[a] Adjusted for age, deprivation, year of diagnosis, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery, tamoxifen, aromatase inhibitors), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (prior use of hormone replacement therapy, oral contraceptives).

[b] CCB usage based on the year prior to breast cancer diagnosis, no adjustment for comorbidities, and non-user group restricted to those who did not receive any anti-hypertensive medication during the exposure period

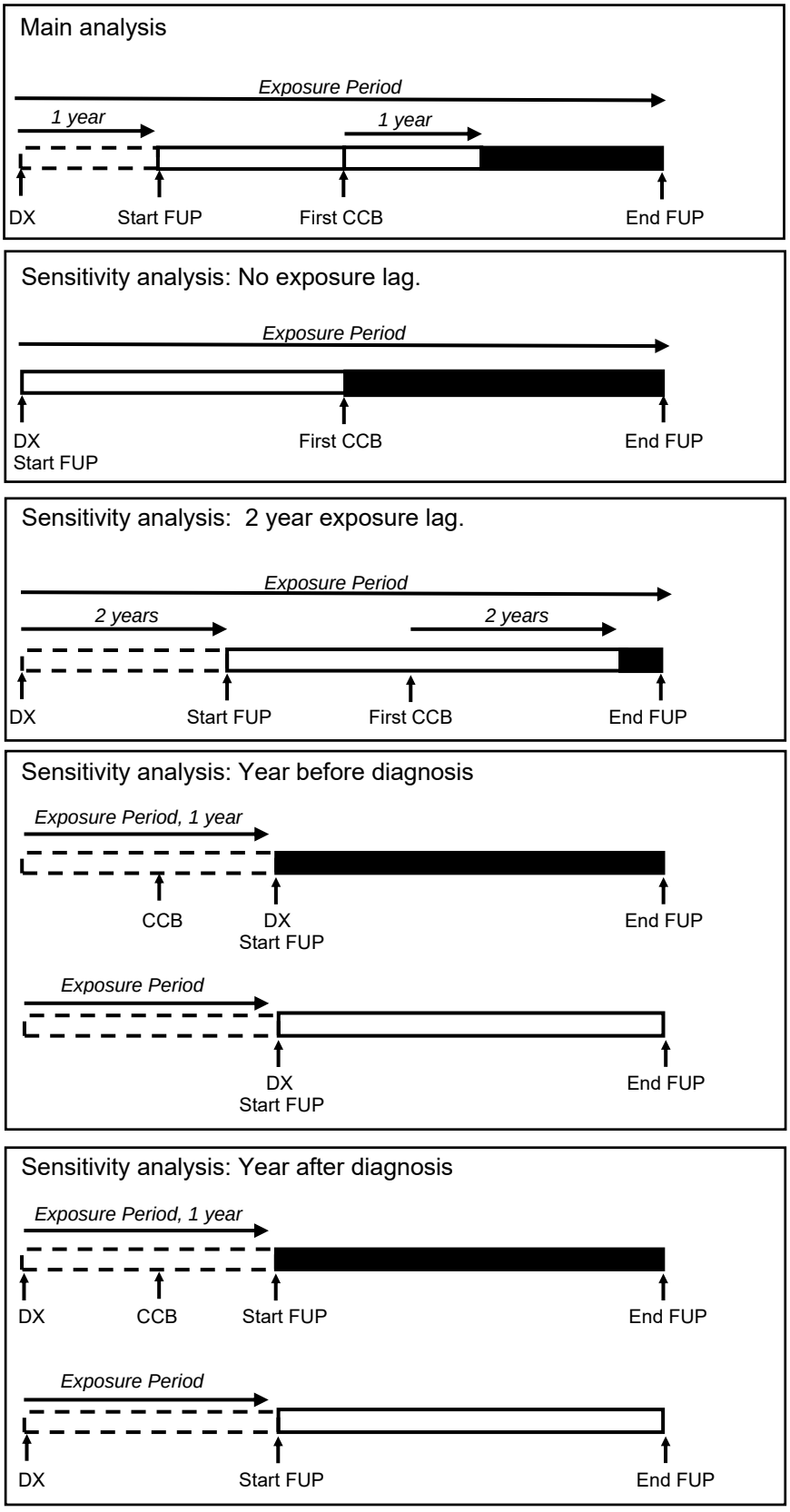
[c] Complete case, additionally adjusted for smoking, obesity and alcohol consumption
[d] Multiply imputed, additionally adjusted for stage and grade
[e] Multiply imputed, additionally adjusted for stage and grade. Restricted to patients included in the Northern & Yorkshire Cancer Registry, which has staging information for over 92% of patients
[f] Except for 'CCB vs. other anti-hypertensive medication' where patients who received a different anti-hypertensive medication serve as the reference group
[g] Deaths with a primary cause of breast cancer unless otherwise stated
[h] Using the Fine and Gray sub-distribution hazard model with non-breast cancer death as competing risk

Appendices

Appendix 1: List of generic and proprietary drug names used to identify calcium channel blocker use

Substance	Medication
Amlodipine	Amlodipine, Amlostin, Exforge, Istin
Diltiazem	Diltiazem, Adizem, Angitil, Dilcardia, Dilzem, Slozem, Tildiem, Viazem, Zemtard
Felodipine	Felodipine, Cardioplen, Felogen, Felotens, Keloc, Neofel, Parmid, Plendil, Triapin, Vascalpha
Isradipine	Isradipine
Lacidipine	Lacidipine, Motens
Lercanidipine	Lercanidipine, Zanidip
Nicardipine	Nicardipine, Cardene
Nifedipine	Nifedipine, Adalat, Adipine, Beta-Adalat, Calchan, Coracten, Fortipine, Kentipine, Nifedipress, Tenif, Tensipine, Valni
Nimodipine	Nimodipine, Nimotop
Verapamil	Verapamil, Cordilox, Securon, Univer, Verapress, Vertab, Zolvera

Appendix 2: Illustration of study design for selected analyses[a]



Legend: Before FUP CCB User CCB Non-user

[a] FUP: follow-up period; DX: breast cancer diagnosis